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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Viswanathan SRINIVASAN et al.

Confirmation No. 4898
Group Art Unit: 1615

Appl. No: : 10/798,884

Examiner: Sasan, Aradhana

Filed : March 12, 2004

For : DOSAGE FORM CONTAINING A MORPHINE DERIVATIVE AND ANOTHER DRUG

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Commissioner for Patents
U.S. Patent and Trademark Office
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401 Dulany Street
Alexandria, VA 22314

Sir:

This Appeal is from the Examiner's Final Rejection of claims 1-21, 23-52, 72-78, 80-87, 92-96 and 99-116 set forth in the Office Action mailed from the U.S. Patent and Trademark Office on October 19, 2007.

A Notice of Appeal in response to the October 19, 2007 Final Office Action was filed on February 19, 2008.

The requisite fee under 37 C.F.R. § 41.20(b)(2) for filing this Appeal Brief (for a Small Entity) is being paid concurrently herewith.

Inasmuch as this Appeal Brief is being filed within the initial two-month period prescribed by 37 C.F.R. § 41.37(a)(1), set to expire April 21, 2008 (April 19/20, 2008 being a Saturday/Sunday), it is believed that no extension of time is required. However, the Patent and Trademark Office is authorized to charge any fee necessary for maintaining the pendency of this application, including any appeal or extension of time fees that may be necessary, to Deposit Account No. 19-0089.

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I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Sovereign Pharmaceuticals, Ltd. of Fort Worth, Texas. The corresponding assignment was recorded in the U.S. Patent and Trademark Office on July 28, 2004 at REEL 015615, FRAME 0519.

II. RELATED APPEALS AND INTERFERENCES

Appellants note that a Notice of Appeal was filed on February 25, 2008 in co-pending and commonly assigned Application No. 10/736,902, which application contains claims over which some of the present claims have provisionally been rejected on the ground of nonstatutory obviousness-type double patenting (see page 14, section 19 of the Final Office Action mailed October 19, 2007). Appellants, Appellants' representative or the Assignee are not aware of any other prior and pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

The status of the claims is as follows:

Claims 1-21, 23-52, 64-68, 70-78, 80-87, 92-96 and 99-116 are pending in this application.

Claims 64-68, 70 and 71 are withdrawn from consideration.

Claims 22, 53-63, 69, 79, 88-91, 97 and 98 are cancelled.

Each of claims 1-21, 23-52, 72-78, 80-87, 92-96 and 99-116 is indicated as rejected in the Final Office Action mailed October 19, 2007.

The rejection of each of claims 1-21, 23-52, 72-78, 80-87, 92-96 and 99-116 is under appeal. Claims 1-21, 23-52, 72-78, 80-87, 92-96 and 99-116 involved in the appeal are reproduced in the Claims Appendix attached hereto.

IV. STATUS OF AMENDMENTS

No Amendment has been filed subsequent to the Final Office Action mailed October 19, 2007.

V. SUMMARY OF CLAIMED SUBJECT MATTER

A. Claim 1

Independent claim 1 is drawn to a pharmaceutical dosage form which comprises (a) a first drug which comprises at least one morphine derivative having antitussive activity and (b) at least one second drug. The dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of the period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

See, e.g., page 2, lines 4-9 from bottom and page 62, lines 3-8 of the present specification.

B. Claim 23

Independent claim 23 is drawn to a bi-layered tablet which comprises a first layer and a second layer. The first layer comprises a first drug comprising at least one morphine derivative having antitussive activity, and the second layer comprises at least

one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines. Further, the bi-layered tablet provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of the period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug.

See, e.g., page 3, line 6 from bottom to page 4, line 2 and page 64, lines 12-19 of the present specification.

C. Claim 39

Independent claim 39 is drawn to a multi-layered tablet which comprises at least a first layer and a second layer. The first layer comprises at least one of codeine, dihydrocodeine, hydrocodone and a pharmaceutically acceptable salt thereof and the second layer comprises at least one drug which is selected from decongestants, expectorants, mucus thinning drugs, analgesics and antihistamines.

See, e.g., page 5, lines 7-12 from bottom and page 66, line 2 from bottom to page 67, line 3 of the present specification.

D. Claim 72

Independent claim 72 is drawn to a pharmaceutical dosage form which comprises (a) a first drug which comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof and has a first plasma half-life and (b) at least one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines and has a second plasma half-life which differs from

the first plasma half-life by at least about 2 hours. The dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 80 % of the period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

See, e.g., page 7, line 2 from bottom to page 8, line 8 and page 71, lines 4-12 of the present specification.

E. Claim 78

Independent claim 78 is drawn to a pharmaceutical dosage form which comprises (a) at least one first morphine derivative in a first form or layer and (b) at least one second morphine derivative which is different from the first morphine derivative in a second form or layer which is different from the first form or layer. The dosage form releases the at least one first morphine derivative over a different period and/or at a different rate than the at least one second morphine derivative.

See, e.g., page 8, lines 12-17 and 20-23, page 17, lines 8-12 and page 72, lines 1-5 and 10-12 of the present specification.

F. Claim 99

Independent claim 99 is drawn to a bi-layered tablet which comprises a first layer and a second layer. The first layer comprises a first drug which is selected from codeine and pharmaceutically acceptable salts thereof, and the second layer comprising at least one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines. Further, the bi-layered tablet provides a plasma concentration

within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of the period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug.

See, e.g., page 3, line 6 from bottom to page 4, line 9 and page 12, lines 1-10 of the present specification.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The broad issues under consideration are:

1. Whether claims 1-3, 18-21, 78, 80 and 92-96 are properly rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fanara et al., U.S. Patent No. 6,699,502 (hereafter "FANARA") and in particular, whether the disclosure of FANARA is sufficient to establish a *prima facie* case of obviousness of the subject matter of claims 1-3, 18-21, 78, 80 and 92-96.

2. Whether claims 4-7, (12-14), 15-17, 23-36, 38-44, 47, 49-52, 72-77, 81-87, 99-111 and 114-116 are properly rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of Jaeger, U.S. Patent No. 3,914,425 (hereafter "JAEGER") and in particular, whether the disclosure of FANARA in view of JAEGER is sufficient to establish a *prima facie* case of obviousness of the subject matter of claims 4-7, 15-17, 23-29, 30-36, 38-44, 47, 49-52, 72-77, 81-87, 99-111 and 114-116.

3. Whether claims 8-11, 37, 45, 46, 112 and 113 are properly rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of JAEGER and further in view of Findlay et al., U.S. Patent No. 4,650,807 (hereafter "FINDLAY") and in particular, whether the disclosure of FANARA in view of FINDLAY in further

view of FINDLAY is sufficient to establish a *prima facie* case of obviousness of the subject matter of claims 8-11, 37, 45, 46, 112 and 113.

Appellants further note that the Examiner has provisionally rejected several of the above claims under the non-statutory doctrine of obviousness-type double patenting as allegedly being unpatentable over certain claims of co-pending Application Nos. 10/736,902, 10/910,806, 10/939,351, 11/012,267, 11/115,293 and 11/115,321. Appellants will address these provisional rejections once the Board has rendered a decision on the above issues 1. to 3.

VII. ARGUMENTS

A. Citation of Authority

Obviousness

The appropriate starting point for a determination of obviousness is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 466 (1966):

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

The test of obviousness *vel non* is statutory and requires a comparison of the claimed subject matter as a whole with the prior art to which the subject matter pertains. *In re Brouwer*, 77 F.3d, 422, 37 U.S.P.Q. 2d 1663 (Fed. Cir. 1996); *In re Ochiai*, 71 F.3d 1565, 37 U.S.P.Q. 2d 1127 (Fed. Cir. 1995).

Often, it will be necessary to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. This analysis should be made explicit. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741. "A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id*, at 1741.

"If the Examiner fails to establish a *prima facie* case, the rejection is improper and will be overturned." *In re Rijckaert*, 9 F.3d, 1532, 28 U.S.P.Q.2d, 1956 (Fed. Cir. 1993), citing *In re Fine*, 837 F.2d 1071, 1074,5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

B. Claims 1-3, 18-21, 78, 80 and 92-96 Are Not Properly Rejected Under 35 U.S.C. 103(a) As Unpatentable Over FANARA

1. Summary of Rejection

The rejection mainly relies on col. 2, lines 36-50 of FANARA where it allegedly is taught to simultaneously administer more than one active substance and combining the

therapeutic effects of active substances with different pharmacokinetic profiles. The rejection asserts that "[i]n order to have the combined therapeutic effects of active substances, it would have been obvious to one with ordinary skill in the art that the period of therapeutic effectiveness of the first active substance would be coextensive with the period of therapeutic effectiveness of the second active substance, especially if the two active substances are related to similar (antitussive) therapeutic activities." Page 9, last sentence of Final Office Action of October 19, 2007.

2. Response

a. FANARA Fails to Render Obvious Independent Claim 1

Appellants respectfully submit that the Examiner's conclusions with respect to FANARA are based on hindsight. In particular, FANARA is concerned primarily with pharmaceutical compositions for the controlled release of active substances (see, e.g., title and col. 1, first paragraph of FANARA), not with the administration of different active substances in a single dosage form and for this reason alone, one of ordinary skill in the art has no reason to consult FANARA for guidance in the latter respect.

The passage of FANARA which the Examiner appears to primarily rely on, i.e., col. 2, lines 36-50, states (emphasis added):

> In parallel, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration. In the case where the same active substance is simultaneously administered for immediate release and for prolonged release, this makes it possible to rapidly release a sufficient dose of active substance to trigger the desired effect and to maintain this effect by a gradual and prolonged release of the same active substance. In the case where an active substance is released immediately and another active substance is released

gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles.

The Examiner appears to take the position that in view of the above passage one of ordinary skill in the art allegedly would have an apparent reason to provide a dosage form which comprises two different active substances, one released immediately after administration and the other one released gradually and regularly after administration, and releases the two active substances in such a manner that the plasma concentration of one active substance is within a therapeutic range over a period which is coextensive with at least about 70 % of the period over which the plasma concentration of the other active substance is within a therapeutic range.

It is noted that the above passage makes reference to active substances which have "very different pharmacokinetic profiles" and can be administered by means of the immediate/controlled release formulations of FANARA. However, FANARA does not explain what exactly is to be understood by the phrase "very different pharmacokinetic profiles". In this regard, it is pointed out that the term "pharmacokinetic profile" encompasses a wide range of properties of a drug.

For example, according to

http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

(see EVIDENCE APPENDIX) the term "pharmacokinetic profile" is defined as "[t]he characteristics of a drug that determine its absorption, distribution and elimination in the body". Appellants are unable to see why the fact that FANARA mentions that the immediate/controlled release combinations set forth therein make it possible to obtain combined therapeutic effects by means of two active substances which have very different absorption, distribution and elimination characteristics in the body allegedly

renders it obvious to one of ordinary skill in the art to use an immediate/controlled release combination for providing plasma concentrations in a therapeutic range of these two active substances in a way such that the therapeutically effective period of one drug overlaps at least about 70 % of the therapeutically effective period of the other drug.

Appellants further are unable to find any other statements in FANARA which would support a conclusion that FANARA renders it obvious to one of ordinary skill in the art to provide the subject matter of present claim 1.

In this regard, it further is noted that the above-cited passage of FANARA must be considered and assessed in the context of the entire disclosure of FANARA.

For example, in lines 15-27 of col. 3, the inventors of FANARA make it clear that their contribution to the art does not rest in the provision of dosage forms which provide immediate/controlled release of two different active substances but rather that their invention consists in the provision of a new matrix composition for the controlled release part of corresponding dosage forms (and, primarily, for dosage forms which consist of only a single, controlled release composition), which matrix composition has certain advantages.

Specifically, the inventors of FANARA acknowledge that "orally administrable solid pharmaceutical compositions combining, in a single unit, a portion exhibiting immediate release and a portion exhibiting delayed release have been described" but allege that these compositions are difficult to make and are not available in the desired form for each and every active substance. It further is stated in FANARA that the controlled release matrix compositions disclosed therein "do not

require excessive quantities of matrix excipients and allow regular and continuous release of active substances over periods of at least 12 hours."

Accordingly, one of ordinary skill in the art will understand that FANARA neither teaches nor suggests combined immediate/controlled release dosage forms which are different from the known dosage forms in any respect other than the composition of the matrix for the controlled release portion thereof.

Further, FANARA does not at all convey the impression that immediate/controlled release dosage forms are advantageous or even only suitable for each and every combination of two active substances. For example, in the passage from col. 5, line 39 to col. 6, line 26 FANARA states (emphasis added):

> According to a specific embodiment of the invention, the controlled-release pharmaceutical compositions according to the invention are used in combination with one or more pharmaceutical compositions allowing immediate release of active substances. When these two types of compositions are present in the same unit, this makes it possible to obtain, in a single administration, both the immediate release of a first active substance and the prolonged release of the same or of a second active substance.
>
> Accordingly, the present invention also relates to pharmaceutical compositions which can be administered orally, comprising
>
> A. at least one layer comprising an active substance and excipients which allow immediate release of the said active substance after administration, and
> B. at least a second layer which allows the controlled release of the same or of a second active substance, comprising the said same or second active substance, at least one matrix-type excipient and at least one alkalinizing agent.
>
> [...]
>
> Such combined pharmaceutical compositions can be prepared according to various methods known to persons skilled in the art.
>
> More particularly, these combined pharmaceutical compositions may be provided in the form of a tablet in which at least one layer A is stuck to at least one layer B.
>
> [...]
>
> <u>The multilayer tablets are particularly well suited to cases of combinations of active substances for which very specific beneficial therapeutic effects have recently been obtained, for example, pseudoephedrine/cetirizine,</u>

hydrocodone/acetaminophen, immediate release hydrocodone/prolonged release hydrocodone.

The embodiments referred to by FANARA in the last paragraph of the above passage are illustrated in Example 4 (double-layer tablet containing controlled-release pseudoephedrine and immediate release cetirizine) and Example 7 (double-layer tablet containing hydrocodone in both a controlled-release layer and an immediate release layer).

The fact that FANARA mentions only a few very specific examples of combinations of active substances for which the immediate/controlled release dosage forms (multilayer tablets) mentioned therein may be "particularly well suited" rather than pointing out that these multilayer tablets are advantageous with respect to the administration of any combination of two active substances is a clear indication that the inventors of FANARA were not at all concerned about the overlap of the periods of therapeutic effectiveness of these active substances. This is further supported by, e.g., Table 10 in col. 10 of FANARA which compares the time-dependent release of the two active substances (pseudoephedrine and cetrizine) in the double-layer tablet of Example 4 but fails to provide any information whatsoever regarding the duration of action of these two active substances, let alone regarding the overlap in the periods of therapeutic effectiveness thereof.

At any rate, there is not even a single passage in FANARA wherein the duration of action of any active substance is addressed. Whenever combinations of active substances are mentioned in FANARA these combinations are to be contained in immediate release/controlled release dosage forms, i.e., dosage forms which are designed

for the sole purpose of providing different release rates and/or release periods of the active substances, i.e., without any concern regarding the time and duration of action of one active substance in relation to the time and duration of action of the other active substance. This fact alone should make it apparent that FANARA is unable to render obvious the subject matter of claim 1, i.e., a claim which addresses, in terms of plasma concentrations within a therapeutic range, the relationship (overlap) between the time and duration of action (period of therapeutic effectiveness) of one particular type of drug (i.e., a morphine derivative having antitussive activity) and the time and duration of action of another (second) drug which is comprised in the same dosage form.

Appellants further point out that the Examiner apparently was unable to cite any document which in combination with FANARA could be considered to render it obvious to one of ordinary skill in the art to use the immediate/controlled release dosage forms set forth in FANARA for providing a plasma concentration within a therapeutic range of one drug over a period which is coextensive with at least about 70 % of the period over which the plasma concentration of any other drug (and specifically, a morphine derivative having antitussive activity) is in the therapeutic range.

In view of the foregoing, it is submitted that the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter recited in present independent claim 1 (and any of the claims dependent therefrom) with respect to FANARA.

b. FANARA Fails to Render Obvious Independent Claim 78

Claim 78 essentially recites that the pharmaceutical dosage form set forth therein comprises at least two different morphine derivatives in two different forms or layers and

that the dosage form releases these at least two different morphine derivatives at different rates and/or over different periods.

FANARA mentions a combination of immediate release hydrocodone and prolonged release hydrocodone in col. 6, lines 24/25 and illustrates in Example 7 thereof a double-layer tablet which comprises hydrocodone bitartrate in both an immediate release layer and a controlled release layer.

In comparison, instant claim 78 encompasses, *inter alia*, a combination which comprises (at least) two different morphine derivatives which are released at different rates and/or over different periods. FANARA neither teaches nor suggests that the hydrocodone in one of the layers of the double-layer tablet of Example 7 can or should be replaced by a different morphine derivative and for this reason alone, fails to render obvious the subject matter of present independent claim 78 (and any of the claims dependent therefrom) as well.

C. Claims 4-7, (12-14), 15-17, 23-36, 38-44, 47, 49-52, 72-77, 81-87, 99-111 and 114-116 Are Not Properly Rejected Under 35 U.S.C. 103(a) As Unpatentable Over FANARA in View of JAEGER

1. Summary of Rejection

The rejections appear to concede that FANARA alone does not render obvious the subject matter of the rejected claims but alleges that JAEGER cures the deficiencies of FANARA in this regard. Specifically, the rejection relies on Example 2 of JAEGER which allegedly illustrates a three-layer "pill" or tablet containing codeine phosphate. The rejection further asserts that JAEGER also teaches preparations which contain codeine and additional drugs such as antihistamines, decongestants and expectorants.

2. Response

a. FANARA in View of JAEGER Fails to Render Obvious Independent Claim 23

What claim 23 has in common, *inter alia,* with independent claim 1 is that it also recites a pharmaceutical dosage form, i.e., a bi-layered tablet, which comprises a first drug comprising at least one morphine derivative having antitussive activity and at least one second drug (i.e., a drug selected from decongestants, expectorants, mucus thinning drugs, and antihistamines) whose period of plasma concentration within a therapeutic range is coextensive with at least about 70 % of the period over which the plasma concentration of the first drug is within a therapeutic range.

As set forth in detail above in section VII.B.2.a. with respect to independent claim 1, FANARA fails to render it obvious to one of ordinary skill in the art to provide an (intermediate/controlled release) dosage form which releases two different drugs in a way such that the therapeutically effective period of one drug overlaps the therapeutically effective period of the other drug by at least about 70 %.

JAEGER is unable to cure this deficiency of FANARA and for this reason alone, the subject matter of present claim 23 is not rendered obvious by a combination of these two documents.

Specifically, JAEGER teaches that 6-amino-2-methyl-2-heptanol (heptaminol), a relatively non-toxic compound lacking antitussive effects of its own, can enhance the effect of codeine so that the codeine dosage and the associated side effects may be reduced sharply while achieving a desired antitussive effect (col. 1, lines 11-17). Example 2 of JAEGER describes a three-layer pill wherein each of the layers contains both heptaminol and codeine phosphate. JAEGER also mentions that the compositions

described therein may additionally contain antihistamines, expectorants and decongestants. In particular, in col. 3, lines 3-12, JAEGER states:

> Conventional cold preparations containing codeine may additionally contain antihistamines such as triprolidine hydrochloride, decongestants such as pseudoephedrine hydrochloride, and expectorants, such as glyceryl guaiacolate. 40 Percent of the codeine in such preparations may be replaced by heptaminol according to this invention without decreasing antitussive potency while reducing the side effects of the codeine. The heptaminol may benefit the patient by contributing its known physiological effects.

Appellants are unable to see how the above passage of JAEGER can render it obvious to combine codeine (phosphate) and an antihistamine, decongestant or expectorant in a dosage form (in particular, a bi-layered tablet) which provides the codeine and the second drug in way such that the period of plasma concentration within a therapeutic range of the antihistamine, decongestant or expectorant is coextensive with at least about 70 % of the period over which the plasma concentration of codeine is within a therapeutic range, and neither does the Final Office Action offer any explanation in this regard.

Appellants submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of present independent claim 23 (and any of the claims dependent therefrom) over FANARA in view of JAEGER.

b. FANARA in View of JAEGER Fails to Render Obvious Independent Claim 39

Independent claim 39 is drawn essentially to a multi-layered tablet which comprises at least one layer that comprises codeine, dihydrocodeine and/or hydrocodone

(including pharmaceutically active salts thereof) and at least one other layer which comprises a decongestant, an expectorant, a mucus thinning drug, an analgesic and/or an antihistamine.

The Examiner appears to acknowledge that FANARA by itself does not render obvious the multi-layered tablet recited in present claim 39 but seems to take the position that JAEGER cures the deficiencies of FANARA in this regard.

Appellants submit that neither FANARA nor JAEGER teaches or suggests any multi-layered tablet which comprises a layer that contains a morphine derivate and a separate layer which comprises a decongestant, an expectorant, a mucus thinning drug, an analgesic and/or an antihistamine. In fact, the only multi-layered (bi-layered) tablets illustrated in FANARA contain either a single drug, i.e., hydrocodone (bitartrate) (see Example 7) or a combination of an antihistamine and a decongestant (Example 4). In this regard, it also has to be taken into account that FANARA is primarily concerned with dosage forms which comprise only a single drug in a single matrix composition, as discussed above.

One of the Examples of JAEGER (Example 2) describes a three-layered tablet, all three layers of which contain codeine phosphate and heptaminol (in different amounts), but no other drug. JAEGER also mentions merely in passing (see the passage in col. 3 cited above in the context of claim 23) that the cold preparations described therein (Examples 1 and 3 describe coated single-layer tablets and a syrup, respectively) may optionally contain an additional drug selected from antihistamines, decongestants and expectorants. However, these facts alone do not provide an apparent reason for one of

ordinary skill in the art to incorporate an antihistamine, decongestant and/or expectorant into the three-layered tablet of Example 2.

It is submitted that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of claim 39 over FANARA in view of JAEGER as well.

c. FANARA in View of JAEGER Fails to Render Obvious Independent Claim 72

What claim 72 has in common, *inter alia,* with independent claim 1 is that it also recites a pharmaceutical dosage form which comprises a first drug comprising at least one morphine derivative having antitussive activity (in particular, codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof) and at least one second drug (in particular, a drug selected from decongestants, expectorants, mucus thinning drugs, and antihistamines) whose period of plasma concentration within a therapeutic range is coextensive with at least about 70 % (in particular, at least about 80 %) of the period over which the plasma concentration of the first drug is within the therapeutic range. Compared to claim 1, claim 72 additionally recites that the at least one second drug has a plasma half-life which differs from the plasma half-life of the first drug by at least about 2 hours.

As set forth in detail in section VII.B.2.a. with respect to independent claim 1, FANARA fails to render it obvious to one of ordinary skill in the art to provide an (intermediate/controlled release) dosage form which releases two different drugs in such a way that the therapeutically effective period of one drug overlaps the therapeutically effective period of the other drug by at least about 70 %.

Further, as set forth in detail in section VII.C.2.a. with respect to independent claim 23, JAEGER is unable to cure the deficiencies of FANARA and for this reason alone, the subject matter of present claim 72 is not rendered obvious by a combination of these two documents.

In addition, neither FANARA nor JAEGER addresses any plasma half-lives, let alone any difference in the plasma half-lives of two drugs which are combined in a single dosage form.

In view of the foregoing, it is submitted that the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of independent claim 72 (and any of the claims dependent therefrom) with respect to FANARA in view of JAEGER as well.

d. FANARA in View of JAEGER Fails to Render Obvious Independent Claim 99

Independent claim 99 differs from independent claim 23 in that according to claim 99 the "at least one morphine derivative having antitussive activity" recited in claim 23 is replaced by a specific morphine derivative, i.e., "codeine and pharmaceutically acceptable salts thereof".

Accordingly, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter recited in present independent claim 99 (and any of the claims dependent therefrom) with respect to FANARA in view of JAEGER for at least all of the reasons which are set forth in detail in section VII.C.2.a. with respect to claim 23, which reasons are referred to herein their entirety in order to avoid repetition.

e. FANARA in View of JAEGER Fails to Render Obvious Dependent Claims 12-14

Claims 12-14 all depend, directly or indirectly, from independent claim 1 and essentially recite, *inter alia*, that the plasma half-life of the at least one second drug recited in claim 1 differs from the plasma half-life of the at least one first drug recited in claim 1 by at least about 2, 3 or 4 hours respectively.

The Examiner apparently concedes that FANARA by itself is unable to render obvious the subject matter of claims 12-14 but appears to be of the opinion that JAEGER cures the deficiencies of FANARA in this regard.

Appellants submit that JAEGER is completely silent as to the plasma half-life of any drug mentioned therein (and so is FANARA), let alone mentions any difference between the plasma half-lives of two drugs. For this reason alone, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of present claims 12-14 over FANARA in view of JAEGER.

f. FANARA in View of JAEGER Fails to Render Obvious Dependent Claim 26

Claim 26 is dependent from claim 24 which in turn depends from independent claim 23 and essentially recites that the bi-layered tablet of claim 23 comprises (a) at least one of codeine, dihydrocodeine, hydrocodone, and pharmaceutically acceptable salts thereof as the at least one morphine derivative having antitussive activity and (b) at least two of phenylephedrine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin, and pharmaceutically acceptable salts thereof as the at least one second drug.

Applicants fail to see that FANARA and/or JAEGER teaches or suggests corresponding drug combinations, let alone in connection with a disclosure that the therapeutically effective periods of the drugs (b) are to overlap the therapeutically effective periods of drugs (a) by at least about 70 %.

Appellants submit that for at least the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of claim 26, even if one were to assume, *arguendo*, that the subject matter of claims 23 and 24 is rendered obvious by FANARA in view of JAEGER.

g. FANARA in View of JAEGER Fails to Render Obvious Dependent Claim 33

Claim 33 is dependent from independent claim 23 and essentially recites that both layers of the bi-layered tablet of claim 23 are controlled release layers.

Appellants note that the disclosure of FANARA which relates to multi-layered tablets appears to be limited to combinations which comprise both an immediate release layer and a controlled release layer.

JAEGER does not address multi-layered tablets in general terms but discloses a three-layered tablet which appears to comprise an outer immediate release layer and two inner controlled release layers. In addition to differing from the tablet of Example 2 of JAEGER in that it is only a bi-layered tablet which does not comprise an immediate release layer, the bi-layered tablet of instant claim 33 comprises at least one second drug (in a controlled release layer) selected from decongestants, expectorants, mucus thinning

drugs, and antihistamines whereas the tablet of Example 2 of JAEGER comprises only a single drug, i.e., codeine phosphate.

Appellants submit that for at least all of the foregoing reasons, FANARA in view of JAEGER fails to render obvious the subject matter of present claim 33, even if one were to assume, *arguendo*, that the Examiner has succeeded in establishing a *prima facie* case of obviousness of independent claim 23.

h. FANARA in View of JAEGER Fails to Render Obvious Dependent Claim 47

Claim 47 is dependent from independent claim 39 and essentially recites that the at least one drug which is selected from decongestants, expectorants, mucus thinning drugs, analgesics and antihistamines and is present in the second layer of the multi-layered tablet of claim 39 has a plasma half-life which differs from the plasma half-life of the at least one of codeine, dihydrocodeine, hydrocodone, and pharmaceutically acceptable salts thereof which is present in the first layer of the multi-layered tablet by at least 1 hour.

Appellants submit that both FANARA and JAEGER are completely silent as to the plasma half-life of any drug mentioned therein, let alone mention any difference between the plasma half-lives of two drugs. For this reason alone, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of claim 47 over FANARA in view of JAEGER, even if one were to assume, *arguendo*, that the subject matter of independent claim 39 is rendered obvious by these two documents.

i. FANARA in View of JAEGER Fails to Render Obvious Dependent Claims 48 and 49

Claim 48 is dependent from claim 47 which in turn is dependent from independent claim 39 and essentially recites that (a) the at least one drug which is selected from decongestants, expectorants, mucus thinning drugs, analgesics and antihistamines and is present in the second layer of the multi-layered tablet of claim 39 has a plasma half-life which differs from the plasma half-life of the at least one of codeine, dihydrocodeine, hydrocodone, and pharmaceutically acceptable salts thereof present in the first layer by at least 1 hour and (b) that the therapeutically effective period of the at least one drug in the second layer overlaps the therapeutically effective period of the at least one drug in the first layer by at least about 80 %.

Claim 49 depends from claim 48 and additionally recites that the at least one drug in the second layer comprises one or more of phenylephrine, pseudoephedrine, chlorpheniramine, and pharmaceutically acceptable salts thereof.

It is pointed out that both FANARA and JAEGER are completely silent as to the plasma half-life of any drug mentioned therein, let alone mention any difference between the plasma half-lives of two drugs. Additionally, as set forth in detail in sections VII.B.2.a. and VII.C.2.a. above with respect to independent claims 1 and 23, neither FANARA nor JAEGER address any overlap in the therapeutically active periods of two drugs which are provided by the same dosage form.

Appellants submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of claim 48 (and claim 49 dependent therefrom) over FANARA in view of JAEGER, even if one

were to assume, *arguendo*, that the subject matter of both independent claim 39 and dependent claim 47 is rendered obvious by these two documents.

In this regard, Appellants point out that the Final Office Action mailed October 19, 2007 does not even specifically mention claim 48, let alone explain why this claim allegedly is rendered obvious by FANARA in view of JAEGER.

j. FANARA in View of JAEGER Fails to Render Obvious Dependent Claim 102

Claim 102 is dependent from independent claim 99 (through claim 100) and essentially recites that the bi-layered tablet of claim 99 comprises (a) codeine phosphate and (b) at least two of phenylephedrine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin, and pharmaceutically acceptable salts thereof as the at least one second drug.

Applicants fail to see that FANARA and/or JAEGER teaches or suggests corresponding drug combinations, let alone in connection with a disclosure that the therapeutically effective periods of the drugs (b) are to overlap the therapeutically effective periods of drug (a) by at least about 70 %.

Appellants submit that for at least the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of claim 102, even if one were to assume, *arguendo*, that the subject matter of claims 99 and 100 is rendered obvious by FANARA in view of JAEGER.

k. FANARA in View of JAEGER Fails to Render Obvious Dependent Claim 109

Claim 109 is dependent from independent claim 99 and essentially recites that both layers of the bi-layered tablet of claim 99 are controlled release layers.

Appellants note that the disclosure of FANARA which relates to multi-layered tablets appears to be limited to combinations which comprise both an immediate release layer and a controlled release layer.

JAEGER does not address multi-layered tablets in general terms but discloses a three-layered tablet which appears to comprise an outer immediate release layer and two inner controlled release layers. In addition to differing from the tablet of Example 2 of JAEGER in that it is only a bi-layered tablet which does not comprise an immediate release layer, the bi-layered tablet of instant claim 109 comprises at least one second drug (in a controlled release layer) selected from decongestants, expectorants, mucus thinning drugs, and antihistamines whereas the tablet of Example 2 of JAEGER comprises only a single drug, i.e., codeine phosphate.

Appellants submit that for at least all of the foregoing reasons, FANARA in view of JAEGER fails to render obvious the subject matter of present claim 109, even if one were to assume, *arguendo*, that the Examiner has succeeded in establishing a *prima facie* case of obviousness of independent claim 99.

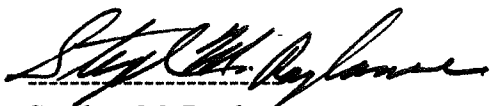
D. Claims 8-11, 37, 45 and 46 Are Not Properly Rejected Under 35 U.S.C. 103(a) As Unpatentable Over FANARA in View of JAEGER in Further View of FINDLAY

Appellants note that claims 8-11, 37, 45 and 46 depend, directly or indirectly, from independent claims 1 (claims 8-11), 23 (claim 37) and 39 (claims 45 and 46). As set forth above in detail in sections VII.B.2.a., VII.C.2.a. and VII.C.2.b., neither of claims 1, 23 and 39 is rendered obvious by FANARA or FANARA in view of JAEGER. It is submitted that for this reason alone, the Examiner has failed to establish a *prima facie* case of obviousness of dependent claims 8-11, 37, 45 and 46 over FANARA in view of JAEGER in further view of FINDLAY.

VIII. CONCLUSION

Appellants respectfully submit that, for at least all of the foregoing reasons the Examiner has failed to establish a *prima facie* case of obviousness of rejected claims 1-21, 23-52, 72-78, 80-87, 92-96 and 99-116, which is a prerequisite for maintaining a rejection under 35 U.S.C. § 103. The Board is, therefore, respectfully requested to reverse the Final Rejection, and to allow the application to issue in its present form.

Respectfully submitted,
Viswanathan SRINIVASAN et al.



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CLAIMS APPENDIX

1. A pharmaceutical dosage form which comprises (a) a first drug which comprises at least one morphine derivative having antitussive activity and (b) at least one second drug, wherein the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

2. The dosage form of claim 1, wherein the at least one of morphine derivative comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

3. The dosage form of claim 2, wherein the first drug comprises at least one of codeine phosphate, dihydrocodeine bitartrate and hydrocodone bitartrate.

4. The dosage form of claim 2, wherein the first drug comprises codeine phosphate.

5. The dosage form of claim 2, wherein the at least one second drug comprises at least one of a decongestant, expectorant, mucus thinning drug, and antihistamine.

6. The dosage form of claim 1, wherein the at least one second drug comprises a decongestant.

7. The dosage form of claim 6, wherein the second drug comprises at least one of phenylepherine, pseudoephedrine and pharmaceutically acceptable salts thereof.

8. The dosage form of claim 2, wherein the at least one second drug comprises an antihistamine.

9. The dosage form of claim 8, wherein the antihistamine comprises at least one of chlorpheniramine, promethazine, carbinoxamine and pharmaceutically acceptable salts thereof.

10. The dosage form of claim 1, wherein the at least one second drug comprises an expectorant.

11. The dosage form of claim 10, wherein the expectorant comprises guaifenesin.

12. The dosage form of claim 5, wherein a plasma half-life of the at least one second drug differs from a plasma half-life of the first drug by at least about 2 hours.

13. The dosage form of claim 3, wherein a plasma half-life of the at least one second drug differs from a plasma half-life of the first drug by at least about 3 hours.

14. The dosage form of claim 1, wherein a plasma half-life of the at least one second drug differs from a plasma half-life of the first drug by at least about 4 hours.

15. The dosage form of claim 5, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 80 % of the period of a plasma concentration within the therapeutic range of the first drug.

16. The dosage form of claim 2, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 90 % of the period of a plasma concentration within the therapeutic range of the first drug.

17. The dosage form of claim 1, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 95 % of the period of a plasma concentration within the therapeutic range of the first drug.

18. The dosage form of claim 1, wherein the dosage form comprises a tablet.

19. The dosage form of claim 18, wherein the tablet comprises at least two layers.

20. The dosage form of claim 19, wherein the tablet is a bi-layered tablet.

21. The dosage form of claim 18, wherein the tablet comprises a matrix which comprises the first drug and has dispersed therein particles which comprise the at least one second drug.

23. A bi-layered tablet which comprises a first layer and a second layer, the first layer comprising a first drug which comprises at least one morphine derivative having antitussive activity, and the second layer comprising at least one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines, wherein the bi-layered tablet provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug.

24. The bi-layered tablet of claim 23, wherein the first layer comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

25. The bi-layered tablet of claim 24, wherein the second layer comprises at least one of phenylepherine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin and pharmaceutically acceptable salts thereof.

26. The bi-layered tablet of claim 24, wherein the tablet comprises at least two of phenylepherine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin and pharmaceutically acceptable salts thereof.

27. The bi-layered tablet of claim 23, wherein the first layer only comprises one or more of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof as active ingredient(s).

28. The bi-layered tablet of claim 24, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 80 % of the period of a plasma concentration within the therapeutic range of the first drug.

29. The bi-layered tablet of claim 25, wherein the period of a plasma concentration within a therapeutic range of the at least one second drug is coextensive with at least about 90 % of the period of a plasma concentration within a therapeutic range of the first drug.

30. The bi-layered tablet of claim 23, wherein at least one of the first and second layers is an immediate release layer.

31. The bi-layered tablet of claim 30, wherein the first layer is an immediate release layer.

32. The bi-layered tablet of claim 30, wherein the second layer is an immediate release layer.

33. The bi-layered tablet of claim 23, wherein both of the first and second layers are controlled release layers.

34. The bi-layered tablet of claim 24, wherein the first layer comprises a total of from about 0.1 mg to about 120 mg of at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

35. The bi-layered tablet of claim 34, wherein the first layer comprises a total of from about 5 mg to about 90 mg of at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

36. The bi-layered tablet of claim 35, wherein the first layer comprises a total of from about 25 mg to about 50 mg of at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

37. The bi-layered tablet of claim 34, wherein the second layer comprises at least one of (i) from about 0.1 mg to about 16 mg of chlorpheniramine maleate or an equivalent amount of at least one other pharmaceutically acceptable salt of chlorpheniramine; (ii) from about 1 mg to about 90 mg of phenylepherine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of phenylepherine; (iii) from about 1 mg to about 240 mg of pseudoephedrine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of pseudoephedrine; (iv) from about 0.1 mg to about 75 mg of promethazine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of promethazine; (v) from about 0.1 mg to about 32 mg of carbinoxamine maleate or an equivalent amount of at least one other pharmaceutically acceptable salt of carbinoxamine; and (vi) form about 1

mg to about 2400 mg of guaifenesin or an equivalent amount of at least one pharmaceutically acceptable salt of guaifenesin.

38. The bi-layered tablet of claim 35, wherein the first layer comprises at least one of (i) from about 1 mg to about 90 mg of phenylepherine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of phenylepherine; and (ii) from about 1 mg to about 240 mg of pseudoephedrine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of pseudoephedrine, and the second layer comprises at least one of an antihistamine and an expectorant.

39. A multi-layered tablet which comprises at least a first layer and a second layer, wherein the first layer comprises at least one of codeine, dihydrocodeine, hydrocodone and a pharmaceutically acceptable salt thereof and the second layer comprises at least one drug which is selected from decongestants, expectorants, mucus thinning drugs, analgesics and antihistamines.

40. The multi-layered tablet of claim 39, wherein the first layer is an immediate release layer.

41. The multi-layered tablet of claim 39, wherein the first layer is a controlled release layer.

42. The multi-layered tablet of claim 41, wherein the second layer is a controlled release layer.

43. The multi-layered tablet of claim 39, wherein the first layer comprises at least one of codeine phosphate, dihydrocodeine bitartrate and hydrocodone bitartrate.

44. The multi-layered tablet of claim 42, wherein the first layer does not contain any active ingredient which is different from codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

45. The multi-layered tablet of claim 39, wherein the tablet comprises at least one of dextromethorphan, phenylepherine, pseudoephedrine, guaifenesin, chlorpheniramine, carbinoxamine, promethazine and pharmaceutically acceptable salts thereof.

46. The multi-layered tablet of claim 39, wherein the tablet comprises at least two of dextromethorphan, phenylepherine, pseudoephedrine, guaifenesin, chlorpheniramine, carbinoxamine, promethazine and pharmaceutically acceptable salts thereof.

47. The multi-layered tablet of claim 39, wherein the at least one drug in the second layer has a plasma half-life which differs by at least about 1 hour from a plasma half-life of the at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

48. The multi-layered tablet of claim 47, wherein the tablet provides a plasma concentration within a therapeutic range of the at least one drug in the second layer over a period which is coextensive with at least about 80 % of a period over which the tablet provides a plasma concentration within a therapeutic range of the at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

49. The multi-layered tablet of claim 48, wherein the at least one drug in the second layer comprises one or more of phenylepherine, pseudoephedrine, chlorpheniramine and pharmaceutically acceptable salts thereof.

50. The multi-layered tablet of claim 39, wherein the layers are discrete zones which are arranged adjacent to each other.

51. The multi-layered tablet of claim 39, wherein the second layer is partially or completely surrounded by the first layer.

52. The multi-layered tablet of claim 39, wherein the second layer is coated with the first layer.

72. A pharmaceutical dosage form which comprises (a) a first drug which comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof and has a first plasma half-life and (b) at least one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines and

has a second plasma half-life which differs from the first plasma half-life by at least about 2 hours, wherein the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 80 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

73. The dosage form of claim 72, wherein the first plasma half-life differs by at least about 3 hours from the second plasma half-life.

74. The dosage form of claim 72, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 90 % of the period over which the dosage form provides a plasma concentration within the therapeutic range of the first drug.

75. The dosage form of claim 74, wherein the dosage form comprises a multi-layered tablet.

76. The dosage form of claim 72, wherein the dosage form is associated with instructions to administer the dosage form three or fewer times per day.

77. The dosage form of claim 75, wherein the dosage form is associated with instructions to administer the dosage form once or twice per day.

78. A pharmaceutical dosage form which comprises (a) at least one first morphine derivative in a first form or layer and (b) at least one second morphine derivative which is different from the first morphine derivative in a second form or layer which is different from the first form or layer, wherein the dosage form releases the at least one first morphine derivative at least one of over a different period and at a different rate than the at least one second morphine derivative.

80. The dosage form of claim 78, wherein the at least one first morphine derivative and the at least one second morphine derivative are independently selected from codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

81. The dosage form of claim 80, wherein the at least one first morphine derivative and the at least one second morphine derivative comprise at least one of codeine phosphate, dihydrocodeine bitartrate and hydrocodone bitartrate.

82. The dosage form of claim 78, wherein the dosage form comprises codeine phosphate.

83. The dosage form of claim 80, wherein the first form or layer is an immediate release form or layer and the second form or layer is a controlled release form or layer.

84. The dosage form of claim 78, wherein the dosage form is a multi-layered tablet which comprises at least one immediate release layer and at least one controlled release

layer which independently comprise at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

85. The dosage form of claim 84, wherein the dosage form further comprises at least one additional drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines.

86. The dosage form of claim 85, wherein at least the immediate release layer thereof comprises the at least one additional drug.

87. The dosage form of claim 85, wherein at least the controlled release layer thereof comprises the at least one additional drug.

92. The dosage form of claim 78, wherein the dosage form releases the at least one first morphine derivative over a different period and at a different rate than the at least one second morphine derivative.

93. The dosage form of claim 78, wherein the dosage form releases the at least one first morphine derivative over a different period than the at least second morphine derivative.

94. The dosage form of claim 93, wherein the dosage form releases the at least one first morphine derivative over a first period and the at least one second morphine

derivative over a second period and not more than about 30 % of the second period are coextensive with all or a part of the first period.

95. The dosage form of claim 94, wherein there is substantially no overlap between the first and second periods.

96. The dosage form of claim 78, wherein the dosage form releases the at least one first morphine derivative at a different rate than the at least second morphine derivative.

99. A bi-layered tablet which comprises a first layer and a second layer, the first layer comprising a first drug which is selected from codeine and pharmaceutically acceptable salts thereof, and the second layer comprising at least one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines, wherein the bi-layered tablet provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug.

100. The bi-layered tablet of claim 99, wherein the first layer comprises codeine phosphate.

101. The bi-layered tablet of claim 100, wherein the second layer comprises at least one of phenylepherine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin and pharmaceutically acceptable salts thereof.

102. The bi-layered tablet of claim 100, wherein the tablet comprises at least two of phenylepherine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin and pharmaceutically acceptable salts thereof.

103. The bi-layered tablet of claim 99, wherein the first layer comprises only one or more of codeine and pharmaceutically acceptable salts thereof as active ingredient(s).

104. The bi-layered tablet of claim 99, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 80 % of the period of a plasma concentration within the therapeutic range of the first drug.

105. The bi-layered tablet of claim 100, wherein the period of a plasma concentration within a therapeutic range of the at least one second drug is coextensive with at least about 90 % of the period of a plasma concentration within a therapeutic range of the first drug.

106. The bi-layered tablet of claim 99, wherein at least one of the first and second layers is an immediate release layer.

107. The bi-layered tablet of claim 106, wherein the first layer is an immediate release layer.

108. The bi-layered tablet of claim 106, wherein the second layer is an immediate release layer.

109. The bi-layered tablet of claim 99, wherein both of the first and second layers are controlled release layers.

110. The bi-layered tablet of claim 99, wherein the first layer comprises a total of from about 5 mg to about 90 mg of at least one of codeine and a pharmaceutically acceptable salt thereof.

111. The bi-layered tablet of claim 99, wherein the first layer comprises a total of from about 25 mg to about 50 mg of at least one of codeine phosphate.

112. The bi-layered tablet of claim 110, wherein the second layer comprises at least one of (i) from about 0.1 mg to about 16 mg of chlorpheniramine maleate or an equivalent amount of at least one other pharmaceutically acceptable salt of chlorpheniramine; (ii) from about 1 mg to about 90 mg of phenylepherine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of phenylepherine; (iii) from about 1 mg to about 240 mg of pseudoephedrine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of

pseudoephedrine; (iv) from about 0.1 mg to about 75 mg of promethazine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of promethazine; (v) from about 0.1 mg to about 32 mg of carbinoxamine maleate or an equivalent amount of at least one other pharmaceutically acceptable salt of carbinoxamine; and (vi) form about 1 mg to about 2400 mg of guaifenesin or an equivalent amount of at least one pharmaceutically acceptable salt of guaifenesin.

113. The bi-layered tablet of claim 111, wherein the first layer comprises at least one of (i) from about 1 mg to about 90 mg of phenylepherine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of phenylepherine; and (ii) from about 1 mg to about 240 mg of pseudoephedrine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of pseudoephedrine, and the second layer comprises at least one of an antihistamine and an expectorant.

114. The dosage form of claim 4, wherein the second drug comprises at least one drug selected from phenylepherine, pseudoephedrine and pharmaceutically acceptable salts thereof.

115. The dosage form of claim 4, wherein the at least one second drug comprises at least one drug selected from chlorpheniramine, promethazine, carbinoxamine and pharmaceutically acceptable salts thereof.

116. The dosage form of claim 4, wherein the at least one second drug comprises guaifenesin.

EVIDENCE APPENDIX

http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

downloaded from the Internet on July 5, 2007 and submitted with Amendment filed July 31, 2007

RELATED PROCEEDINGS APPENDIX

None.

http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

Glossary

β-DYSTROGLYCAN The α- and β-dystroglycans are the laminin-binding components of the dystrophin–glycoprotein complex, which provides a linkage between the subsarcolemmal cytoskeleton and the extracellular matrix.

ACETYLCHOLINE A neurotransmitter ($C_7H_{17}NO_3$) that is released at autonomic synapses and neuromuscular junctions. It is active in the transmission of nerve impulses and is formed enzymatically in tissues from choline.

AMINOGLYCOSIDES A group of antibiotics (such as gentamicin) that inhibit bacterial protein synthesis and are particularly active against Gram-negative bacteria.

CYTOTOXICITY The properties of a virus, transgene, vector, compound or molecule that are toxic for cells.

CpG ISLAND Genomic regions that are rich in the CpG pattern, are resistant to methylation and are often associated with promoter activity.

DEPENDOVIRUS A single-stranded DNA virus from the family parvoviridae (subfamily parvovirinae), which is dependent on a co-infection with helper adenoviruses or herpes viruses for efficient replication.

DYSTROBREVINS The components of the dystrophin–glycoprotein complex that bind to syntrophin and (indirectly) to the C-terminal of dystrophin. Dystrobrevin-α recruits signalling proteins, such as neuronal nitric oxide synthase.

ELECTROPORATION The application of an electric current to the plasma membrane of a cell, to temporarily open pores or channels through which DNA might pass.

EPISOMES DNA that can replicate autonomously in the cytoplasm of host cells.

EXTRACELLULAR MATRIX In muscle, this is a thin layer (basal lamina) that contains collagen, elastin and fibronectin, which surrounds each muscle fibre. This might act as a semipermeable filter or a selective cellular barrier and is important in regeneration after damage.

F-ACTIN A protein that is involved in the contractile apparatus and the maintenance of the cytoskeleton of myofibres.

HEK-293 CELLS Host cells that generate viral particles following transfection with the rAAV plasmid and the helper plasmid.

IMMUNOGENICITY The properties of a virus, transgene, vector, compound or molecule that provoke an immune response.

MICROBUBBLES Encapsulated gas microbubbles that can be used as drug or gene carriers, which are able to penetrate into the smallest membranes. When exposed to sufficiently high-amplitude ultrasound, the microbubbles rupture and release the drugs and genes that are contained in their encapsulating layer.

MYOBLAST TRANSPLANTATION The implantation of exogenous muscle-progenitor cells into muscle to generate new myofibres or to support existing myofibres.

NEO-ANTIGEN A foreign (transgene) product that is able to stimulate an immune response.

PHARMACOKINETIC PROFILE The characteristics of a drug that determine its absorption, distribution and elimination in the body.

PRE-mRNA SPLICING The removal of introns from the precursor mRNA molecule; the remaining exons are spliced together.

PRESSURIZED ISOLATED-LIMB PERFUSION The introduction of therapeutic agents under pressure in a limb after isolation of the blood circulation by clamping.

PRIMARY MUSCLE-CELL CULTURES Cells that are taken into culture directly from a tissue biopsy. In contrast to cell lines that only contain immortalized cells, these

cultures contain heterogeneous cell populations.

RNaseH Ribonuclease H. An enzyme that cleaves RNA/DNA complexes.

SARCOLEMMA The membrane that encloses a striated muscle fibre.

SPECTRIN A large contractile submembrane protein that, similar to dystrophin, contains an actin-binding domain and a long repeat domain.

SPLICEOSOMAL COMPLEX A large dynamic complex that consists of small nuclear RNA molecules and protein components. It mediates the two catalytic steps of the splicing reaction: the excision of introns from the pre-mRNA and the ligation of the two exon termini.

SYNTROPHINS Peripheral membrane proteins that bind to the C-terminal of dystrophin, which might have a role in the process of synaptogenesis.

TRANSDUCTION The transfer of genetic material into a cell using a viral vector.

TRANSFECTION The transfer of exogenous DNA into a cell.